Cigarette smoking is associated with increased rates of morbidity and mortality, and among patients with established cardiovascular disease, smoking status is a strong independent risk factor for all-cause mortality, cardiovascular mortality, cancer mortality, cardiovascular events, and bleeding risk. Cigarette smoking has a number of adverse effects that influence the cardiovascular system. Importantly, smoking causes endothelial dysfunction, dyslipidemia, and increased platelet activation, which leads to a prothrombotic state.1

The platelet P2Y\textsubscript{12} receptor is the major platelet receptor that mediates adenosine diphosphate-induced platelet activation and aggregation processes.3 The key role of this platelet signaling pathway in atherothrombotic processes is underscored by the multitude of studies demonstrating the clinical benefit associated with P2Y\textsubscript{12} receptor blockade, particularly in high-risk settings such as patients with acute coronary syndromes (ACS) and undergoing percutaneous coronary interventions (PCI).3 Clopidogrel is still the most widely used P2Y\textsubscript{12} receptor inhibitor,4 but, despite its clinical benefits, it has several limitations mostly attributed to its broad variability in individual response profile leading to sizeable rates of patients with inadequate antiplatelet protection, who are at increased risk of atherothrombotic events, including stent thrombosis.5,6 However, although smokers have overall higher event rates compared with non-smokers, clinical studies have shown that clopidogrel therapy is associated with a greater relative benefit among smokers (Figure 1).7–10 Several factors have been suggested to explain this “smoker’s paradox”. First, platelets from smoking patients with coronary artery disease have higher surface P2Y\textsubscript{12} receptor density and enhanced response to clopidogrel compared with non-smokers.11 Increased surface P2Y\textsubscript{12} density can contribute to the higher risk for recurrent events among smokers compared with non-smokers, and can explain observations on the better relative benefit of clopidogrel among smokers.12 Second, smoking is an inducer of cytochrome P450 (CYP) 1A2 and CYP2B6, hepatic enzymes involved in the metabolism of clopidogrel.10 This in turn may enhance generation of clopidogrel’s active metabolite, leading to greater pharmacodynamic (PD) effects.7,10,11 Moreover, a dose-response effect on clopidogrel-induced antiplatelet activity among smokers has been observed, whereby heavy smokers, objectively assessed by cotinine (the predominant metabolite of nicotine) levels assessments, had the greatest platelet inhibitory effects and the lowest rates of high on-treatment platelet reactivity (Figure 2).13

In this issue of the Journal, Kodaira et al14 report their results of data collected from a registry cohort (Japan Cardiovascular Database-Keio interhospital Cardiovascular Studies) of 6,195 ACS patients undergoing PCI treated with clopidogrel.

![Figure 1. Hazard ratios (95% confidence interval) for major adverse cardiovascular events (MACE) in clinical trials with clopidogrel according to smoking status. Forest plots represent current non-smokers (Upper) and smokers (Bottom). MACE and follow-up duration were defined according to each clinical trial. (Adapted with permission from Zhao ZG, et al.7)](image-url)
to the lower risk profile, smokers appeared to have a relative higher clinical benefit from clopidogrel compared with non-smokers. However, several factors need to be taken into account when interpreting the findings from this study, which are mainly related to the registry design and the retrospective nature of the analysis. First, the study lacks an objective assessment of smoking status, as cotinine levels were not measured. Accordingly, a stratification of smoking status into heavy or light smokers based on level of nicotine exposure, or at least on the number of smoked cigarettes, was not performed. Moreover, the authors pooled together current smokers with patients who had smoked anytime during the year before the index PCI. Because cigarette smoking induces CYP1A2 activity in a dose-related manner, and because of the dose-response effect of smoking on clopidogrel-induced antiplatelet effects, a more precise classification of the patients may have provided further insights in data interpretation. Second, the study did not account for the variability in CYP1A2 activity among smokers, which may affect the response to clopidogrel.

The authors should be commended for this study as they provide data from a very large cohort of all comers ACS patients undergoing PCI and showed that, although the “smoker’s paradox” was largely explained by confounding factors related to smoking status, the lower risk profile of smokers may be a result of a higher clopidogrel response. This suggests that smoking status should be considered in the selection of patients for clopidogrel therapy.
not evaluate the influence of genetic polymorphisms of the CYP2C19 enzyme. Given the well-known association between loss-of-function and gain-of-function alleles with clopidogrel response profiles in terms of thrombotic and bleeding events, respectively, a different distribution of CYP polymorphisms in the 2 groups may have affected clinical outcomes. Indeed, this has further relevance because of the high prevalence of loss-of-function polymorphisms in Asian populations. Third, the authors did not collect PD data. The availability of data on platelet inhibition by clopidogrel in the 2 groups would have provided important mechanistic insights to corroborate the study findings. In addition, the short duration of the follow-up (approximately 9 days), as well as the absence of data on stent thrombosis and cardiovascular mortality rates, reduced the ability of the study to detect clinically meaningful findings and did not allow any conclusion on the effects of smoking on the long-term antiplatelet effects of clopidogrel. Finally, patients were treated exclusively with clopidogrel. The newer generation P2Y₁₂ receptor inhibitors, prasugrel and ticagrelor, are characterized by more potent platelet inhibitory effects than clopidogrel, which translates into better net clinical benefit in ACS patients compared with clopidogrel. These findings have led to updates in practice guidelines where, in the absence of contraindications, these agents are recommended as the treatment of choice in ACS patients. Of note, recent observations from clinical trials suggest that prasugrel and ticagrelor may have differential effects according to smoking status.

In particular, in high-risk medically managed ACS patients a significantly enhanced treatment effect with prasugrel among smokers was observed. In contrast, no treatment effect was observed with ticagrelor among smoking patients, which had consistent superiority over clopidogrel. All studies, however, have consistently shown that recurrent atherothrombotic event rates among smokers remain high, despite the improved outcomes with these novel agents, underscoring the need for well-performed large-scale registries to help define the most effective antiplatelet strategy for these high-risk patients.

In conclusion, although smoking is a well-known major risk factor for atherothrombotic heart disease, at the same time, in clopidogrel-treated patients, smoking seems to exhibit a “paradoxical benefit”, bringing to mind the two-sided personality of Dr Jekyll and Mr Hyde, where one side is good and the other is evil.

References